PATENT
071949-2106

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: BUECHLER et al.

Title: NOVEL METHODS FOR THE ASSAY OF TROPONIN I AND T AND COMPLEXES OF TROPONIN I AND T AND SELECTION OF ANTIBODIES FOR USE IN IMMUNOASSAYS

Appl. No.: 09/687,051

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Examiner: G. Gabel

Art Unit: 1641

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APPEAL BRIEF

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Sir:

Applicants (herein, "Appellants") hereby appeal the Final Rejection of claims 69, 70, and 79-93. This Appeal Brief is accompanied by the requisite fee set forth in 37 C.F.R. § 1.17(c). If this fee is incorrect or if any additional fees are due in this regard, please charge or credit our Deposit Account No. 50-0872 for the appropriate amount.

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Real Party in Interest

The real party in interest in this appeal is Biosite, Inc. (formerly Biosite Diagnostics, Inc.), which is the assignee of the present application.

Related Appeals and Interferences

A Notice of Appeal has been submitted in related U.S. Patent Application No. 09/349,194, together with a submission responsive to a final rejection. Substantially the same issues presented in the present Appeal Brief are pending in the related application. As of this writing, no response has been received to Applicants' submission in the related application.

Status of Claims

On June 24, 2003, Appellants filed a Notice of Appeal from the Examiner's Action of March 24, 2003, making final the rejection of claims 69, 70, and 79-93. The Examiner has indicated that claims 71-74 are allowable as written, and claims 84, 85, 90, and 93 would be allowable if written in independent form. Claims 69, 70, and 79-93 stand finally rejected under 35 U.S.C. §112, first paragraph, for allegedly failing to satisfy the enablement requirement. Claims 1-68 and 75-78 have been cancelled without prejudice.

Status of Amendments

In response to the Examiner's invitation to rewrite claims 84, 85, 90, and 93 in independent form, Appellants submitted an amendment after-final on June 24, 2003 canceling claims 84, 85, 90, and 93, and adding new claims 94-98 to present the subject matter of the cancelled claims in the suggested independent form. In addition, Appellants amended claims 79-81 and 88 solely in order to remove a potential ambiguity in these claims. In an Advisory Action

dated July 22, 2003, the amendment was denied entry by the Examiner. The Examiner also indicated that the after-final amendment would not be entered upon the filing of an appeal brief.

Summary of The Invention

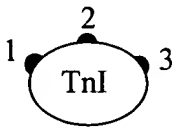
The present invention relates to antibodies that specifically bind to cardiac specific troponin I in both free and complexed forms. In particular, the instant claims relate to antibodies that are "insensitive with respect to" or that "bind to" each cardiac troponin I form selected from the following group: (i) free troponin I, (ii) troponin I in binary complexes with troponin C, and (iii) troponin I in ternary complexes with troponin C and troponin T; to methods for selecting such antibodies; and to compositions comprising such antibodies. The antibodies referred to in the claims may be provided on solid phases and as members of an antibody pair comprising a solid phase antibody and a labeled antibody for use in immunoassays.

Troponin is a protein complex that is involved in regulating muscle contraction. The troponin complex is composed of three separate polypeptides, known as troponin I, troponin T, and troponin C. Specification, page 3, lines 29-30. Troponin exists in muscle mainly as a complex comprising all three troponin polypeptides – a so-called "ternary complex." *Id.*, page 5, lines 6-10. When muscle cells are damaged (such as occurs in skeletal muscle following exercise, or in cardiac muscle following a myocardial infarction), the contents of the muscle cells, including troponin, are released into the blood. For this reason, the ability to identify troponin released from heart muscle into the blood can provide a simple, rapid means of diagnosing myocardial infarction in a patient suspected of having suffered such an event. *Id.*, page 2, line 30, through page 3, line 28.

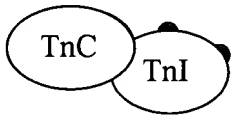
The amount of skeletal and smooth muscle in the body, however, is far in excess of the amount of heart muscle; thus, any assay designed to identify cardiac damage based upon the presence or amount of muscle components in the blood must be able to identify the cardiac components separate from the background of their skeletal and smooth muscle counterparts. Immunoassays generally rely on the use of antibodies that can specifically bind an analyte of interest for detection within a sample containing many other components. In the case of troponin, immunoassays have been developed to identify cardiac troponin through "cardiac-specific" regions of troponin I and T; that is, regions that differ on cardiac troponin I and T in comparison to the same regions on skeletal or smooth muscle troponin I and T. *Id.*, page 3, lines 18-28. Such immunoassays can be formulated in a variety of ways, including "sandwich" immunoassays, "competitive binding" immunoassays, and other assays well known in the art. A signal from the immunoassay is detected and related to the presence or amount of the analyte.

As noted above, troponin exists in muscle mainly as a "ternary complex" comprising all three troponin polypeptides. *Id.*, page 5, lines 6-10. What was not understood prior to the present invention was that cardiac-specific troponin I and troponin T circulates in the blood in forms other than the ternery complex I/T/C. The inventors were the first to describe circulating free cardiac-specific isoforms (*i.e.*, troponin I and troponin T that are free of any other troponin polypeptides), and binary complexes (troponin I/T complex, troponin I/C complex, and/or troponin T/C complex), in addition to the ternary complexe known in the art. Furthermore, the "complex state" of troponin I and T may change over time in a patient, *e.g.*, due to binding of free cardiac-specific isoforms to other circulating troponin polypeptides. *Id.*, page 16, line 16, through page 17, line 19.

The present invention also recognized for the first time that immunoassays that fail to consider the "complex state" of cardiac-specific troponin may not detect all of the cardiac-specific isoform of interest. Taking troponin I as an example, this polypeptide contains certain antigenic sites that are "cardiac-specific." These regions may be present as numbered in this schematic drawing:



Binding of another troponin polypeptide, *e.g.*, troponin C, may obscure one or more of these cardiac-specific regions so that it is not accessible to antibodies directed to that site:



If antibodies directed to region 1 were used in a troponin I immunoassay, the troponin I concentration of the sample measured in the immunoassay may be incorrectly low, due to an inability to detect troponin I in complexes. Such aberrant assay results could end up in in a misdiagnosis of patients. *Id.*, page 17, lines 26-30. On the other hand, selection of antibodies for use in an immunoassay that are directed to region 1 could be used to differentiate free troponin I from complexed troponin I forms, as such antibodies would not recognize troponin I in a binary complex. Assays that can identify all of the troponin I in a sample, whatever the form, and assays that distinguish free cardiac-specific troponin isoforms from complexed isoforms or that

distinguish the binary from ternary complexes of tropinin I, each provide clinically important data to caregivers. *Id.*, page 35, lines 17-26.

Issues

1. Whether claims 69, 70, and 79-83, 86-89, 91 and 92 meet the enablement standard of 35 U.S.C. §112, first paragraph.

Grouping of Claims

The claims on appeal are those pending as of the final rejection (Exhibit A) rather than those submitted in the after final amendment (Exhibit B), which have been refused entry in the case. Claims 71-74 stand allowed. Of the rejected claims, claims 69, 70, 79-83, 86-89, 91, and 92 stand or fall together; and claims 84, 85, 90, and 93 stand or fall together. Each of claims 69, 70, 79-83, 86-89, 91, and 92 refer to one or more antibodies that are "insensitive with respect to" (claims 69 and 70) or that "binds to" (claims 79-83, 86-89, 91, and 92) each form of cardiac troponin I selected from the group consisting of free cardiac troponin I, cardiac troponin I in a binary complex with troponin C, and cardiac troponin I in a ternary complex with troponin C and troponin T. Claims 84, 85, 90, and 93, which the Examiner acknowledges would be allowable if rewritten in independent form, refer to pools of two or more antibodies that provide such binding characteristics.

Argument

35 U.S.C. § 112, First Paragraph, Enablement Rejection

The only issue on appeal is an alleged lack of enablement with regard to claims 69, 70, and 79-83, 86-89, 91 and 92. Appellants respectfully submit that the specification, which the Examiner acknowledges is enabling with regard to a pool of antibodies that are insensitive for

("binds to") each of free troponin I, troponin I in binary complexes with troponin C, and troponin I in ternary complexes with troponin C and troponin T, is also enabling with regard to a single antibody that binds to each of the recited cardiac troponin I forms. The rejection is based on the examiner's personal opinion and unsupported conclusory statements, which have been held to a standard for determining compliance with the enablement requirement that does not comport with the settled law. Because the enablement requirement of 35 U.S.C. §112, first paragraph, has been met, Appellants respectfully request that the rejection be withdrawn or reversed.

Applicable legal standard

The standard for determining enablement is whether the specification as filed provides sufficient information as to permit one skilled in the art to make and use the claimed invention. *United States v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). The test of enablement is not whether experimentation is necessary, but rather whether any experimentation that is necessary is undue. *Id.* A considerable amount of experimentation is permitted, provided that it is merely routine, or provided that the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The rejection ignores the evidence of record in favor of the Examiner's personal opinion

The rejected claims refer to one or more antibodies that are "insensitive with respect to" (claims 69 and 70) or that "binds to" (claims 79-83, 86-89, 91, and 92) each of the following troponin I forms: (i) free cardiac troponin I, (ii) cardiac troponin I in a binary complex with troponin C, and (iii) cardiac troponin I in a ternary complex with troponin C and troponin T. The rejection is premised on the Examiner's unsupported assertion that, while the specification is enabling with regard to a pool of antibodies that are insensitive for (binds to) each of free

troponin I, troponin I in binary complexes with troponin C, and troponin I in ternary complexes with troponin C and troponin T, the specification is not enabling with regard to a single antibody that binds to each of the recited cardiac troponin I forms. *See, e.g.*, Paper No. 15, paragraph bridging pages 2 and 3. It should be noted that the claims are not limited to any particular type of antibody, and would encompass both monoclonal antibodies and polyclonal antibodies. It is well known that a polyclonal antibody by definition is a mixture of different monoclonal antibodies. Thus, the examiner's view that the instant specification is enabling with respect to a pool of antibodies requires that a polyclonal antibody of the claims would similarly be enabled. Appellants, therefore, understand the Examiner's enablement rejection to cover monoclonal antibodies falling under the claims rather than polyclonal antibodies falling under the claims.

During prosecution of the instant claims, Appellants provided a declaration of one of skill in the art, Dr. Kenneth F. Buechler, as evidence of enablement of the claimed invention. In the declaration, Dr. Buechler provided a reasoned scientific explanation as to why the skilled artisan, using the specification as a guide and only routine methods that are well known in the art, could practice the instantly claimed invention. The Examiner has not attempted to rebut the conclusions provided by Dr. Buechler in the declaration, or suggested that the reasoning underpinning these conclusions is not scientifically sound. Instead, rather than consider this evidence on its merits, the Examiner has improperly dismissed the declaration on the basis of an improper evidentiary standard, which requires actual data to prove enablement. ("Applicant fails to provide evidentiary showing such as in the form of data, that supports generation [of the antibodies of the claims]"). Paper No. 15, page 10.

Appellants respectfully submit that, by dismissing Appellants' evidence without proper consideration of its weight, the Examiner has failed to consider the evidence as a whole, a

consideration that is fundamental in any determination of enablement. As stated in MPEP § 2164.05, a declaration or affidavit is, itself, evidence that must be considered, and the evidence need not be conclusive, but merely convincing to the skilled artisan. The Examiner compounds this failure by applying an improper legal standard for judging compliance with enablement requirement, asserting that, regardless of the evidence of record, only data showing that the antibodies of the claims have been generated is sufficient to demonstrate enablement. *See, e.g.*, Paper No. 15, page 10, second full paragraph. Appellants respectfully submit that this is not a correct legal standard. As noted in *In re Wands*, the presence of working examples is one consideration in an enablement analysis; it is not the single determinative consideration as the Examiner apparently believes. [1]

As discussed herein, the instant specification describes antibodies that bind to both free and complexed troponin I, and methods for their generation and identification. As stated in MPEP § 2164.04, "it is incumbent on the Patent Office... to explain why it doubts any statement in a disclosure, and to back up its assertions of its own with acceptable evidence or reasoning.... Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." The Examiner has simply not performed this task, which, like consideration of the evidence as a whole, is fundamental in any determination of enablement. As such, the Examiner has not established any reasonable basis for questioning the enablement of the claims.

[1] As discussed hereinafter, the Examiner is also incorrect in asserting that no evidence has been provided that such antibodies have been generated. *See*, section entitled "*Presence of Working Examples," infra.*

When properly considered, the evidence of record demonstrates that the claims satisfy the enablement requirement

Appellants respectfully submit that the following analysis of the factors set forth in *In re Wands* demonstrates that the rejected claims meet the enablement standard of 35 U.S.C. § 112. In contrast, while the Examiner "goes through the motions" of analyzing the *Wands* factors, that analysis relies on personal opinion and unsupported conclusory statements and is applied to a standard for determining compliance with the enablement requirement that does not comport with the settled law.

Nature of the invention

The claims at issues are directed to providing one or more antibodies that are "insensitive with respect to" or that "binds to" each of (i) free cardiac troponin I, (ii) cardiac troponin I in a binary complex with troponin C, and (iii) cardiac troponin I in a ternary complex with troponin C and troponin T; to methods for selecting such insensitive antibodies; and to compositions comprising such insensitive antibodies.

In contrast, the Examiner continues to mischaracterize the invention by maintaining that it is "directed to a cocktail of insensitive antibodies which bind each one of the free, binary complex, and ternary complex isoforms of [cardiac troponin I]" (Paper No. 15, page 3, emphasis added). The Examiner continues to make this characterization despite the fact that the specification as filed states explicitly that the use of a cocktail of antibodies for this purpose is but one embodiment of the instant invention. For example, the specification explicitly states:

> "[t]he immunoassay may be formulated with a cocktail of antibodies to bind all the troponin complexes and the free troponin I and T. Alternatively, the immunoassay can be formulated with specific antibodies that recognize epitopes of the troponin I and T in the complexes and also the unbound troponin I and T. A preferred immunoassay for troponin I or T involves conjugation of an antibody or

> a cocktail of antibodies to a label or signal generator to form an antibody conjugate(s), which are capable of binding to cardiac specific regions of the troponin complexes of troponin I or T and to unbound troponin I or T.

Page 24, line 21, through page 25, line 3. This section and others in the specification clearly indicate that the invention is not limited to "cocktails" of antibodies, as the Examiner contends. Rather than considering the specification and claims, the Examiner instead begins the enablement analysis with a biased personal opinion of the "nature of the invention." In so doing, the Examiner presupposes what conclusion should be reached regarding enablement, and then, improperly, finds agreement with that conclusion.

Appellants also submit that the Examiner's reply to Appellants' arguments in this regard appears to contradict the Examiner's own position. Indeed, the Examiner acknowledges in Paper No. 15, page 9, first full paragraph, that "page 6 of the specification provides that an 'insensitive antibody' is one that will tend to bind more than one form of troponin, i.e. each one of free cTnI, cTnI in a binary complex with troponin C, and cTnI in a ternary complex with troponin C and troponin T, as recited in the claims." It is unclear, therefore, why the Examiner continues to maintain that the invention is directed solely to providing "a cocktail of antibodies." Appellants respectfully submit that the Examiner's statement of the "nature of the invention" is without support of any evidence of record.

State of the prior art

The Examiner has not disagreed with Appellants' view that the prior art fails to disclose any antibodies that are insensitive with respect to each of free troponin I, troponin I in binary complexes with troponin C, and troponin I in ternary complexes with troponin C and troponin T; but that methods for producing antibodies to an antigen of interest are well established in the art.

Level of one of ordinary skill

The Examiner has not disagreed with Appellants that the level of skill in the art of antibody preparation is high, and that methods for producing antibodies to an antigen of interest are considered routine by those of skill in the art. With regard to monoclonal antibodies specifically, the court in *In re Wands* acknowledged that methods for obtaining and screening monoclonal antibodies were well known even in 1980, some 15 years before the original filing date of the present application. 8 USPQ2d at 1406. Thus, all of the methods needed to practice the invention of the claims at issue are readily available to those of ordinary skill in the art.

Predictability in the art

Appellants respectfully submit that the starting materials (the troponin polypeptides) necessary for generation of the recited antibodies are readily available to the skilled artisan. Coupled with the fact that methods for generating both monoclonal and polyclonal antibodies have long been well known and considered routine in the art, the skilled artisan could predictably practice the claimed invention using the instant specification as a guide. As further evidence of this predictability, Appellants submitted the declaration of Dr. Kenneth Buechler, describing why the skilled artisan would reasonably believe that antibodies could be obtained that are insensitive with respect to (or that bind to) each of free troponin I, troponin I in binary complexes with troponin C, and troponin I in ternary complexes with troponin C and troponin T.

As discussed in the Buechler declaration, cardiac specific troponin I contains various antigenic sites. Because certain antigenic sites may remain available for antibody binding regardless of the complex state of troponin I, these sites may be used to bind free troponin I as well as troponin I complexed with troponin C and/or troponin T. Nothing of record, other than

the Examiner's bare personal view, contradicts this reasoned scientific conclusion.

Moreover, the examples described in the instant invention confirm the accuracy of the scientific basis for Dr. Buechler's statements. For example, Example 23, on page 87, line 31, through page 88, line 2, of the specification, describes the selection of antibodies that bind to both free troponin I and to troponin I in a ternary complex with troponin C and troponin T. According to Dr. Buechler, the skilled artisan would understand that antibodies which bind to free troponin I and to troponin I/C/T ternary complex would also be expected to bind to the binary complex of troponin I and troponin C, because the antigenic site on troponin I which is available for binding in the ternary complex would also be expected to be available in the simpler binary complex. *See, e.g.*, drawing on page 3, of Buechler declaration.

Furthermore, while the declaration of Dr. Buechler describes why the skilled artisan would reasonably believe that even a monoclonal antibody could be produced having the requisite specificity, the instant claims are not limited to a monoclonal antibody having a single binding specificity. Instead, the instant specification states on page 8, lines 9-12, that an antibody may also be a polyclonal antibody. As discussed above, such a polyclonal antibody would be considered equivalent to the "antibody pools" which the Examiner acknowledges meet the enablement standard. The skilled artisan would understand that a polyclonal antibody that binds to each of free troponin I, the troponin I/troponin C binary complex, and the troponin I/troponin C/troponin T ternary complex could readily be obtained by immunization of an animal with each of these troponin I forms as described in the specification, *e.g.*, on page 21, lines 3-32, and isolating the antibodies produced.

In contrast to the substantial evidence of predictability provided by Appellants, the Examiner offers only the bare conclusory statement that "there is no predictability" in the art.

See, e.g., Paper No. 15, page 4, second paragraph. Applicant cannot discern any basis for this statement, particularly in view of substantial evidence to the contrary already of record in the case. The Examiner's unsupported conclusion fails to establish a reasonable basis for questioning the enablement provided in the specification. As stated in MPEP § 2164.04, "it is incumbent on the Patent Office... to explain why it doubts any statement in a disclosure, and to back up its assertions of its own with acceptable evidence or reasoning.... Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure."

Considering the objective evidence of record in its entirety, Appellants respectfully submit that the skilled artisan would acknowledge that it would be predictable that the antibodies of the claims at issue could be obtained using the specification as a guide and only routine immunological methods.

The amount of direction or guidance present

The instant specification provides extensive guidance as to how antigens should be prepared, and how antibodies should be screened, in order to obtain antibodies that are insensitive with respect to each of free troponin I, troponin I in binary complexes with troponin C, and troponin I in ternary complexes with troponin C and troponin T. *See, e.g.*, specification, page 21, line 3, through page 24, line 3; Example 22 beginning on page 82; and Example 23, beginning on page 87.

In contrast, the Examiner offers only the conclusory statement that "the specification fails to provide guidance to provide a single insensitive antibody that specifically binds all of the free, binary and ternary complexed isoforms of cTnI." *See, e.g.*, Paper No. 15, page 4, third paragraph.

Again, such a conclusory statement does not establish a reasonable basis for questioning the enablement provided in the specification. Moreover, the Examiner's response to Appellants' evidence (*i.e.*, "nowhere in the specification specifically shows... any generation and selection [of such antibodies]," paper No. 15, page 11, first full paragraph) seeks yet again to apply the improper standard that only data showing that the antibodies of the claims have been generated is sufficient to demonstrate enablement. The question is not whether such antibodies have been generated, as the Examiner suggests; rather, the question is whether the specification enables such antibodies to be generated without undue experimentation. Furthermore, as discussed in the following section of this submission, the Examiner is incorrect that no such antibodies are demonstrated in the specification.

Considering the objective evidence of record in its entirety, Appellants respectfully submit that the skilled artisan would acknowledge that the specification provides extensive guidance for making and using the claimed invention.

Presence of working examples

Example 23 of the instant specification describes antibodies and assays that measure both free and ternary complexes of troponin I. Because these antibodies rely on formation of a sandwich of (labeled antibody)-(analyte)-(biotinylated antibody)-(avidin solid phase) for development of an assay signal, the skilled artisan would acknowledge that both the biotinylated and labeled antibodies must bind to both free and ternary troponin I complexes. This means that the antigenic site on troponin I (to which the antibody binds) was accessible to antibody even when troponinin I was bound to troponin C in the ternary complex. As discussed by Dr. Beuchler, the skilled artisan would understand from this evidence that such antibody would also bind to the binary complex of troponin I and troponin C. *See, e.g.*, drawing on page 3, of

Buechler declaration. Thus, one of ordinary skill in the art would believe that the instant specification provides working examples of antibodies that are insensitive with respect to each of free troponin I, troponin I in binary complexes with troponin C, and troponin I in ternary complexes with troponin C and troponin T.

The Examiner's reply indicates that the Examiner disagrees with this reasoning, which is based on evidence of record and sound scientific principles. However the Examiner provides no evidence or reasoning that is inconsistent with Appellants' evidence. Instead, the Examiner again simply asserts that nowhere in the examples is such an antibody "specifically" provided. Paper No. 15, page 12, first full paragraph. This is yet another application of the Examiner's improper standard for proof of enablement.

Considering the objective evidence of record in its entirety, the skilled artisan would acknowledge that working examples of antibodies that are insensitive with respect to each of free troponin I, troponin I in binary complexes with troponin C, and troponin I in ternary complexes with troponin C and troponin T are provided by the instant specification.

Quantity of experimentation necessary

As described in detail in the Buechler declaration and in Appellants' prior responses, the specification provides detailed methods that utilize readily available starting materials for preparing and identifying antibodies that are insensitive with respect to (that bind to) each of free troponin I, troponin I in binary complexes with troponin C, and troponin I in ternary complexes with troponin C and troponin T. And, as discussed above, the Examiner does not disagree that methods for producing antibodies generally have long been well known and considered routine by those of skill in the art. Taken together, these facts lead to the inescapable conclusion that the

quantity of experimentation necessary is not undue. *See, e.g., In re Wands*, 8 USPQ2d at 1404 (experimentation is not undue if it is merely routine).

In contrast, the totality of the Examiner's analysis on this issue is a conclusory view that "it would require undue amount of experimentation for the skilled artisan to make and use the method as claimed." Paper No. 15, page 5, first full paragraph. Again, such an assertion, unsupported by any evidence or reasoning of record, cannot establish a lack of enablement. Moreover, in response to Appellants' arguments in this regard, the Examiner again relies on an assertion that nowhere in the examples is such an antibody actually demonstrated. Paper No. 15, page 13, first paragraph. But the question is whether the specification enables such antibodies to be generated without undue experimentation, not whether such antibodies have been actually demonstrated. *See* MPEP § 2164.05. Finally, as discussed in the previous section of this submission, the Examiner is incorrect that no such antibodies are provided in the specification. Given these facts, it is apparent that the Examiner's conclusion that any experimentation would be undue is simply an unsupported personal opinion.

The instant claims meet the enablement standard of 35 U.S.C. § 112, first paragraph

In view of the objective evidence of record, and the foregoing analysis of the factors set forth in *In re Wands*, Appellants respectfully submit that that the present claims meet the enablement standard of 35 U.S.C. § 112, first paragraph. The Examiner's opinion to the contrary is not based upon objective evidence of record, but instead is based on personal opinion, unsupported conclusory statements, and application of a standard for determining compliance with the enablement requirement that does not comport with the settled law.

Conclusion

For the reasons discussed above, Appellants respectfully submit that all the claims are in condition for allowance, and respectfully request that the rejections be withdrawn or reversed, and that the claims be allowed to issue.

Respectfully submitted,

By 

Date August 20, 2003

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Appendix A: Text of the Claims Involved in the Appeal

1-68 (Previously cancelled)

69. (Previously added) An antibody or a fragment thereof, immobilized on a solid phase, that specifically binds cardiac troponin I, wherein said antibody is insensitive with respect to each form of cardiac troponin I selected from the group consisting of free cardiac troponin I, cardiac troponin I in a binary complex with troponin C, and cardiac troponin I in a ternary complex with troponin C and troponin T.

70. (Previously added) An antibody, or fragment thereof, conjugated to a signal generating element, that specifically binds cardiac troponin I, wherein said antibody is insensitive with respect to each form of cardiac troponin I selected from the group consisting of free cardiac troponin I, cardiac troponin I in a binary complex with troponin C, and cardiac troponin I in a ternary complex with troponin C and troponin T.

71. (Previously added) A method of selecting antibodies for an immunoassay for cardiac troponin I, the method comprising:

selecting two or more antibodies that, when used in said immunoassay, provide an assay response that is insensitive with respect to each form of cardiac troponin I selected from the group consisting of free cardiac troponin I, cardiac troponin I in a binary compled with troponin C, and cardiac troponin I in a ternary complex with troponin C and troponin T.

72. (Previously added) A method according to claim 71, wherein said two or more antibodies are independently selected from the group consisting of monoclonal antibodies, recombinant antibodies and polyclonal antibodies.

73. (Previously added) A method according to claim 71, wherein said at least two antibodies are selected to provide a signal that is within about 20% for equimolar amounts of each said form of cardiac troponin I.

74. (Previously added) A method according to claim 71, wherein said method comprises selecting two antibodies, each of which is insensitive with respect to each form of cardiac

troponin I selected from the group consisting of free cardiac troponin I, cardiac troponin I in a binary complex with troponin C, and cardiac troponin I in a ternary complex with troponin C and T.

75-78 (Previously cancelled)

79. (Previously added) A composition comprising:

one or more antibodies, or fragments thereof, immobilized on a solid phase, wherein each form of cardiac troponin I selected from the group consisting of free cardiac troponin I, cardiac troponin I in a binary complex with troponin C, and cardiac troponin I in a ternary complex with troponin C and troponin T binds to one or more of said antibodies.

80. (Previously added) A composition comprising:

one or more antibodies, or fragments thereof, conjugated to a signal generating element, wherein each form of cardiac troponin I selected from the group consisting of free cardiac troponin I, cardiac troponin I in a binary complex with troponin C, and cardiac troponin I in a ternary complex with troponin C and troponin T binds to one or more of said antibodies.

81. (Previously added) A method of selecting antibodies to cardiac troponin I, said method comprising:

selecting one or more antibodies, wherein each form of cardiac troponin I selected from the group consisting of free cardiac troponin I, cardiac troponin I in a binary complex with troponin C, and cardiac troponin I in a ternary complex with troponin C and troponin T binds to one or more of said antibodies.

82. (Previously added) The composition of claim 79 or 80, wherein said antibodies are selected from the group consisting of monoclonal antibody, recombinant antibody and polyclonal antibody.

83. (Previously added) The method of claim 81, wherein said antibodies are selected from the group consisting of monoclonal antibody, recombinant antibody and polyclonal antibody.

84. (Previously added) The composition of claim 79 or 80, wherein said antibodies are a pool of two or more antibodies.

85. (Previously added) The method of claim 81, wherein said antibodies are a pool of two or more antibodies.

86. (Previously added) The composition of claim 79 or 80, wherein said antibodies are unable to distinguish between said forms of cardiac troponin I.

87. (Previously added) The method of claim 81, wherein said antibodies are unable to distinguish between said forms of cardiac troponin I.

88. (Previously added) A composition comprising:

one or more first antibodies, or fragments thereof, immobilized on a solid phase, wherein each form of cardiac troponin I selected from the group consisting of free cardiac troponin I, cardiac troponin I in a binary complex with troponin C, and cardiac troponin I in a ternary complex with troponin C and troponin T binds to one or more of said first antibodies; and

one or more second antibodies, or fragments thereof, conjugated to a signal generating element, wherein each form of cardiac troponin I selected from the group consisting of free cardiac troponin I, cardiac troponin I in a binary complex with troponin C, and cardiac troponin I in a ternary complex with troponin C and troponin T binds to one or more of said second antibodies.

89. (Previously added) The composition of claim 88, wherein said first and second antibodies are independently selected from the group consisting of monoclonal antibody, recombinant antibody and polyclonal antibody.

90. (Previously added) The composition of claim 88, wherein said first and second antibodies are a pool of two or more antibodies.

91. (Previously added) A method of selecting antibodies for a sandwich immunoassay, the method comprising:

selecting one or more first antibodies and one or more second antibodies, wherein each form of cardiac troponin I selected from the group consisting of free cardiac troponin I, cardiac troponin I in a binary complex with troponin C, and cardiac troponin I in a ternary complex with troponin C and troponin T binds to one or more of said first and second antibodies.

92. (Previously added) The method of claim 91 wherein said first and second antibodies are independently selected from the group consisting of monoclonal antibody, recombinant antibody and polyclonal antibody.

93. (Previously added) The method of claim 91, wherein said first and second antibodies are a pool of two or more antibodies.

Appendix B: Text of the Claims as Amended in Submission Dated June 24, 2003

1-68 (Previously cancelled)

69. (Previously added) An antibody or a fragment thereof, immobilized on a solid phase, that specifically binds cardiac troponin I, wherein said antibody is insensitive with respect to each form of cardiac troponin I selected from the group consisting of free cardiac troponin I, cardiac troponin I in a binary complex with troponin C, and cardiac troponin I in a ternary complex with troponin C and troponin T.

70. (Previously added) An antibody, or fragment thereof, conjugated to a signal generating element, that specifically binds cardiac troponin I, wherein said antibody is insensitive with respect to each form of cardiac troponin I selected from the group consisting of free cardiac troponin I, cardiac troponin I in a binary complex with troponin C, and cardiac troponin I in a ternary complex with troponin C and troponin T.

71. (Previously added) A method of selecting antibodies for an immunoassay for cardiac troponin I, the method comprising:

selecting two or more antibodies that, when used in said immunoassay, provide an assay response that is insensitive with respect to each form of cardiac troponin I selected from the group consisting of free cardiac troponin I, cardiac troponin I in a binary compled with troponin C, and cardiac troponin I in a ternary complex with troponin C and troponin T.

72. (Previously added) A method according to claim 71, wherein said two or more antibodies are independently selected from the group consisting of monoclonal antibodies, recombinant antibodies and polyclonal antibodies.

73. (Previously added) A method according to claim 71, wherein said at least two antibodies are selected to provide a signal that is within about 20% for equimolar amounts of each said form of cardiac troponin I.

74. (Previously added) A method according to claim 71, wherein said method comprises selecting two antibodies, each of which is insensitive with respect to each form of cardiac

troponin I selected from the group consisting of free cardiac troponin I, cardiac troponin I in a binary complex with troponin C, and cardiac troponin I in a ternary complex with troponin C and T.

75-78 (Previously cancelled)

79. (Amended herein) A composition comprising:

one or more antibodies, or fragments thereof, immobilized on a solid phase, wherein said one or more antibodies or antibody fragments are selected to bind to cardiac troponin I, and wherein each form of cardiac troponin I selected from the group consisting of free cardiac troponin I, cardiac troponin I in a binary complex with troponin C, and cardiac troponin I in a ternary complex with troponin C and troponin T binds to one or more of said antibodies.

80. (Amended herein) A composition comprising:

one or more antibodies, or fragments thereof, conjugated to a signal generating element, wherein said one or more antibodies or antibody fragments are selected to bind to cardiac troponin I, and wherein each form of cardiac troponin I selected from the group consisting of free cardiac troponin I, cardiac troponin I in a binary complex with troponin C, and cardiac troponin I in a ternary complex with troponin C and troponin T binds to one or more of said antibodies.

81. (Amended herein) A method of selecting antibodies to cardiac troponin I, said method comprising:

selecting one or more antibodies that bind to cardiac troponin I, wherein each form of cardiac troponin I selected from the group consisting of free cardiac troponin I, cardiac troponin I in a binary complex with troponin C, and cardiac troponin I in a ternary complex with troponin C and troponin T binds to one or more of said antibodies.

82. (Previously added) The composition of claim 79 or 80, wherein said antibodies are selected from the group consisting of monoclonal antibody, recombinant antibody and polyclonal antibody.

83. (Previously added) The method of claim 81, wherein said antibodies are selected from the group consisting of monoclonal antibody, recombinant antibody and polyclonal antibody.

84. (Cancelled herein)

85. (Cancelled herein)

86. (Previously added) The composition of claim 79 or 80, wherein said antibodies are unable to distinguish between said forms of cardiac troponin I.

87. (Previously added) The method of claim 81, wherein said antibodies are unable to distinguish between said forms of cardiac troponin I.

88. (Amended herein) A composition comprising:

one or more first antibodies, or fragments thereof, immobilized on a solid phase, wherein said one or more first antibodies or antibody fragments are selected to bind to cardiac troponin I, and wherein each form of cardiac troponin I selected from the group consisting of free cardiac troponin I, cardiac troponin I in a binary complex with troponin C, and cardiac troponin I in a ternary complex with troponin C and troponin T binds to one or more of said first antibodies; and

one or more second antibodies, or fragments thereof, conjugated to a signal generating element, wherein said second antibodies or antibody fragments are selected to bind to cardiac troponin I, and wherein each form of cardiac troponin I selected from the group consisting of free cardiac troponin I, cardiac troponin I in a binary complex with troponin C, and cardiac troponin I in a ternary complex with troponin C and troponin T binds to one or more of said second antibodies.

89. (Previously added) The composition of claim 88, wherein said first and second antibodies are independently selected from the group consisting of monoclonal antibody, recombinant antibody and polyclonal antibody.

90. (Cancelled herein)

91. (Previously added) A method of selecting antibodies for a sandwich immunoassay, the method comprising:

selecting one or more first antibodies and one or more second antibodies, wherein each form of cardiac troponin I selected from the group consisting of free cardiac troponin I, cardiac troponin I in a binary complex with troponin C, and cardiac troponin I in a ternary complex with troponin C and troponin T binds to one or more of said first and second antibodies.

92. (Previously added) The method of claim 91 wherein said first and second antibodies are independently selected from the group consisting of monoclonal antibody, recombinant antibody and polyclonal antibody.

93. (Cancelled herein)

94. (New) A composition comprising:

a pool of two or more antibodies, or fragments thereof, immobilized on a solid phase, wherein said two or more antibodies or antibody fragments are selected to bind to cardiac troponin I, and wherein each form of cardiac troponin I selected from the group consisting of free cardiac troponin I, cardiac troponin I in a binary complex with troponin C, and cardiac troponin I in a ternary complex with troponin C and troponin T binds to one or more of said antibodies.

95. (New) A composition comprising:

a pool of two or more antibodies, or fragments thereof, conjugated to a signal generating element, wherein said two or more antibodies or antibody fragments are selected to bind to cardiac troponin I, and wherein each form of cardiac troponin I selected from the group consisting of free cardiac troponin I, cardiac troponin I in a binary complex with troponin C, and cardiac troponin I in a ternary complex with troponin C and troponin T binds to one or more of said antibodies.

96. (New) A method of selecting antibodies to cardiac troponin I, said method comprising:

selecting a pool of two or more antibodies, wherein said two or more antibodies or antibody fragments are selected to bind to cardiac troponin I, and wherein each form of cardiac troponin I selected from the group consisting of free cardiac troponin I, cardiac troponin I in a binary complex with troponin C, and cardiac troponin I in a ternary complex with troponin C and troponin T binds to one or more of said antibodies.

97. (New) A composition comprising:

A first pool of two or more antibodies, or fragments thereof, immobilized on a solid phase, wherein said two or more antibodies or antibody fragments are selected to bind to cardiac troponin I, and wherein each form of cardiac troponin I selected from the group consisting of free cardiac troponin I, cardiac troponin I in a binary complex with troponin C, and cardiac troponin I in a ternary complex with troponin C and troponin T binds to one or more antibodies of said first pool; and

a second pool of two or more antibodies, or fragments thereof, conjugated to a signal generating element, wherein said two or more antibodies or antibody fragments are selected to bind to cardiac troponin I, and wherein each form of cardiac troponin I selected from the group consisting of free cardiac troponin I, cardiac troponin I in a binary complex with troponin C, and cardiac troponin I in a ternary complex with troponin C and troponin T binds to one or more antibodies of said second pool.

98. (New) A method of selecting antibodies for a sandwich immunoassay, the method comprising:

selecting a first pool of two or more antibodies and a second pool of two or more antibodies, wherein said two or more antibodies or antibody fragments are selected to bind to cardiac troponin I, and wherein each form of cardiac troponin I selected from the group consisting of free cardiac troponin I, cardiac troponin I in a binary complex with troponin C, and cardiac troponin I in a ternary complex with troponin C and troponin T binds to one or more antibodies of said first and second pools.